

AMENDMENTS TO THE CLAIMS

1. (CURRENTLY AMENDED) A method for treating neuropathic pain without alleviating acute pain, comprising:

identifying a subject in need of such treatment; and

providing the subject with an effective amount of at least one compound that selectively activates the M(1) receptor subtype, whereby one or more symptoms of the neuropathic pain are reduced and wherein the compound does not alleviate acute pain.

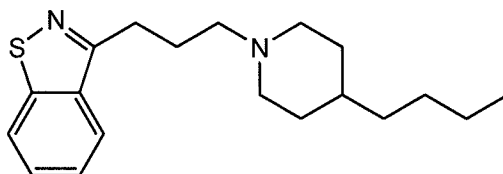
2. (ORIGINAL) The method of claim 1, wherein the subject presents hyperalgesia.

3. (ORIGINAL) The method of claim 1, wherein the subject presents allodynia.

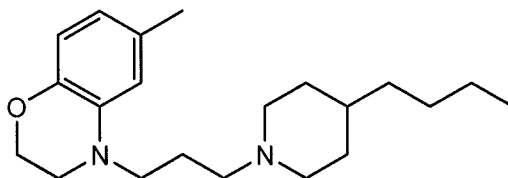
4. (ORIGINAL) The method of claim 1, wherein the neuropathic pain is associated with diabetes, viral infection, irritable bowel syndrome, amputation, cancer, or chemical injury.

5. (CANCELED)

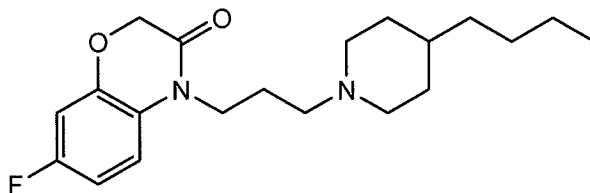
6. (ORIGINAL) The method of claim 1, wherein the compound is selected from the group consisting of the compounds of Formulas VII, VIII, and IX:



(VII)



(VIII)



(IX)

7. (CURRENTLY AMENDED) A method of identifying a compound that alleviates hyperalgesia or allodynia in a subject without alleviating acute pain, comprising:

providing the subject with at least one selective muscarinic receptor test compound; and

determining if the at least one test compound reduces hyperalgesia or allodynia in the subject without alleviating acute pain.

8. (ORIGINAL) The method of claim 7, wherein the at least one test compound is selective for the M(1) or M(4) but not M(2) or M(3) receptor.

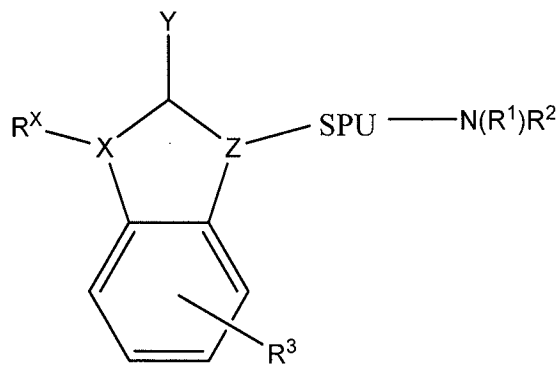
9. (ORIGINAL) The method of claim 7, wherein the at least one test compound is selective for the M(1) receptor.

10. (ORIGINAL) The method of claim 7, wherein the hyperalgesia is thermal hyperalgesia.

11. (ORIGINAL) The method of claim 7, wherein the allodynia is tactile allodynia.

12-13. (CANCELED)

14. (NEW) The method of claim 1, wherein the compound has the structure of formula (I):



(I)

wherein

X is selected from the group consisting of C, O, N and S;

Z is selected from the group consisting of CH and N;

Y is selected from the group consisting of =O, =N and =S or tautomers thereof, such as Y-alkylated tautomers;

SPU is a spacer unit providing a distance d between Z and N wherein —SPU— is a biradical selected from the group consisting of —(CR⁶R⁷)_n—A— and —

C₃₋₈-cycloalkyl-, wherein n is in the range 1 to 5, such as 1, 2, 3, 4, or 5 and A is absent or an optionally substituted —C₃₋₈-cycloalkyl;

N together with R¹ and R² form a heterocyclic ring wherein said heterocyclic ring is selected from the group consisting of perhydroazocine, perhydroazepine, piperidine, pyrrolidine, azetidine, aziridine and 8-azabicyclo[3.2.1]octane and wherein the heterocyclic ring is substituted with one or more substituents R⁴ selected from the group consisting of hydroxy, halogen, C₁₋₈-alkyl, C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylcarbonyl, C₁₋₈-alkylidene, C₂₋₈-alkenyl, C₂₋₈-alkynyl, C₁₋₆-alkyloxyimino, and C₁₋₆-alkyloxyamino each of which may be optionally substituted with a substituent R⁵ and wherein at least one of said substituents R⁴ is R^{4'} selected from the group consisting of C₁₋₈-alkyl, C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylcarbonyl, C₁₋₈-alkylidenec C₁₋₈-alkyloxyimino, and C₁₋₈-alkyloxyamino each of which may be optionally substituted with a substituent R⁵;

R⁵ is selected from the group consisting of hydrogen, halogen, hydroxy, C₁₋₈-alkyl, C₁₋₈-alkoxy, C₃₋₈-cycloalkyl, C₃₋₈-heterocyclyl, C₁₋₈-alkylcarbonyl, C₁₋₈-alkylidene, C₂₋₈-alkenyl and C₂₋₈-alkynyl;

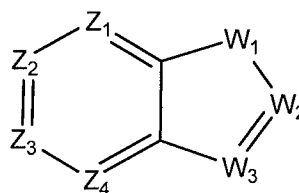
R^x may be absent or selected from the group consisting of hydrogen, optionally substituted C₁₋₈-alkyl, optionally substituted C₃₋₈-cycloalkyl, optionally substituted C₂₋₈-alkenyl, optionally substituted C₂₋₈-alkynyl, optionally substituted aryl, optionally substituted heteroaryl CH₂—N(R⁵)(R⁵), CH₂—OR⁵, CH₂—SR⁵, CH₂—O—C(=O)R⁵, CH₂—O—C(=S)R⁵;

R³ may be present 0-4 times and selected from the group consisting of halogen, hydroxy, optionally substituted C₁₋₈-alkyl, C₁₋₈-alkoxy, optionally substituted C₁₋₈-alkylidene, optionally substituted C₂₋₈-alkenyl, optionally substituted C₂₋₈-alkynyl optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃₋₈-cycloalkyl, optionally substituted C₃₋₈-heterocyclyl, and optionally substituted C₁₋₈-alkylcarbonyl; and

each R⁶ and each R⁷ is independently selected from the group consisting of hydrogen, halogen, hydroxy, optionally substituted C₁₋₈-alkyl, C₁₋₈-alkoxy, optionally substituted C₁₋₈-alkylidene, optionally substituted C₂₋₈-alkenyl, optionally substituted C₂₋

8-alkynyl optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃₋₈-cycloalkyl, optionally substituted C₃₋₈-heterocyclyl, and optionally substituted C₁₋₈-alkylcarbonyl.

15. (NEW) The method of claim 1, wherein the compound has the structure of formula (II):



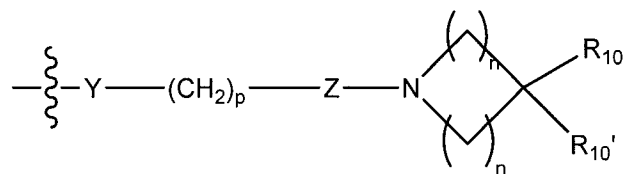
(II)

wherein:

Z₁ is CR₁ or N, Z₂ is CR₂ or N, Z₃ is CR₃ or N, and Z₄ is CR₄ or N, where no more than two of Z₁, Z₂, Z₃ and Z₄ are N;

W₁ is O, S, or NR₅, one of W₂ and W₃ is N or CR₆, and the other of W₂ and W₃ is CG; W₁ is NG, W₂ is CR₅ or N, and W₃ is CR₆ or N; or W₁ and W₃ are N, and W₂ is NG;

G is of formula (III):



(III)

Y is O, S, CHOH, —NHC(O)—, —C(O)NH—, —C(O)—, —OC(O)—, —(O)CO—, —NR₇—, —CH=N—, or absent;

p is 1, 2, 3, 4 or 5;

Z is CR₈R₉ or absent;

each t is 1, 2, or 3;

each R₁, R₂, R₃, and R₄, independently, is H, amino, hydroxyl, halo, or straight- or branched-chain C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, —CN, —CF₃—OR₁₁, —COR₁₁, —NO₂, —SR₁₁, —NHC(O)R₁, —C(O)NR₁₂R₁₃, —NR₁₂R₃, —NR₁₁C(O)NR₁₂R₁₃, —SO₂NR₁₂R₁₃, —OC(O)R₁₁, —O(CH₂)_qNR₁₂R₁₃, or —

$(\text{CH}_2)_q\text{NR}_{12}\text{R}_{13}$, where q is an integer from 2 to 6, or R_1 and R_2 together form —NH—N=N— or R_3 and R_4 together form —NH—N=N— ;

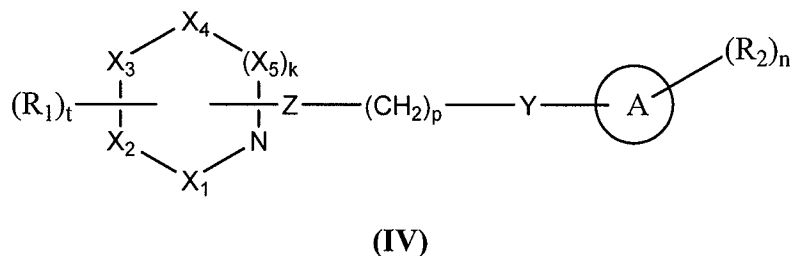
each R_5 , R_6 , and R_7 , independently, is H, C_{1-6} alkyl; formyl; C_{3-6} cycloalkyl; C_{5-6} aryl, optionally substituted with halo or C_{1-6} alkyl; or C_{5-6} heteroaryl, optionally substituted with halo or C_{1-6} alkyl; each R_8 and R_9 , independently, is H or straight- or branched-chain C_{1-8} alkyl;

R_{10} is straight- or branched-chain C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkylidene, C_{1-8} alkoxy, C_{1-8} heteroalkyl, C_{1-8} aminoalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxycarbonyl, C_{1-8} hydroxyalkoxy, C_{1-8} hydroxyalkyl, —SH , C_{1-8} alkylthio, $\text{—O—CH}_2\text{—C}_{5-6}$ aryl, —C(O)—C_{5-6} aryl substituted with C_{1-3} alkyl or halo, C_{5-6} aryl, C_{5-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heterocycloalkyl, $\text{—NR}_{12}\text{R}_{13}$, $\text{—C(O)NR}_{12}\text{R}_{13}$, $\text{—NR}_{11}\text{C(O)NR}_{12}\text{R}_{13}$, $\text{—CR}_{11}\text{R}_{12}\text{R}_{13}$, —OC(O)R_{11} , $\text{—(O)(CH}_2)_s\text{NR}_{12}\text{R}_{13}$ or $\text{—(CH}_2)_s\text{NR}_{12}\text{R}_{13}$, s being an integer from 2 to 8;

R_{10}' is H, straight- or branched-chain C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkylidene, C_{1-8} alkoxy, C_{1-8} heteroalkyl, C_{1-8} aminoalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxycarbonyl, C_{1-8} hydroxyalkoxy, C_{1-8} hydroxyalkyl, or C_{1-8} alkylthio; each R_{11} , independently, is H, straight- or branched-chain C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{2-8} heteroalkyl, C_{2-8} aminoalkyl, C_{2-8} haloalkyl, C_{1-8} alkoxycarbonyl, C_{2-8} hydroxyalkyl, —C(O)—C_{5-6} aryl substituted with C_{1-3} alkyl or halo, C_{5-6} aryl, C_{5-6} heteroaryl, C_{5-6} cycloalkyl, C_{5-6} heterocycloalkyl, $\text{—C(O)NR}_{12}\text{R}_{13}$, $\text{—CR}_5\text{R}_{12}\text{R}_{13}$, $\text{—(CH}_2)_t\text{NR}_{12}\text{R}_{13}$, t is an integer from 2 to 8; and

each R_{12} and R_{13} , independently, is H, C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{5-6} aryl, optionally substituted with halo or C_{1-6} alkyl; or C_{5-6} heteroaryl, optionally substituted with halo or C_{1-6} alkyl; or R_{12} and R_{13} together form a cyclic structure; or a pharmaceutically acceptable salt, ester or prodrug thereof.

16. (NEW) The method of claim 1, wherein the compound has the structure of formula (IV):



wherein

X_1, X_2, X_3, X_4 and X_5 are selected from C, N and O;

k is 0 or 1;

t is 0, 1 or 2;

R_1 is straight or branched-chain C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkylidene, C_{1-8} alkoxy, C_{1-8} heteroalkyl, C_{1-8} aminoalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxycarbonyl, C_{1-8} hydroxyalkoxy, C_{1-8} hydroxyalkyl, --SH, C_{1-8} alkylthio, --O--CH₂--
 C_{5-6} aryl, --C(O)-- C_{5-6} aryl substituted with C_{1-3} alkyl or halo; C_{5-6} aryl or C_{5-6} cycloalkyl optionally comprising 1 or more heteroatoms selected from N, S and O; --C(O)NR₃ R₄, --NR₃ R₄, --NR₃ C(O)NR₄ R₅, --CR₃ R₄, --OC(O)R₃, --(O)(CH₂)_s NR₃ R₄ or --(CH₂)_s NR₃ R₄;

where R₃, R₄ and R₅ are the same or different, each independently being selected from H, C_{1-6} alkyl; C_{5-6} aryl optionally comprising 1 or more heteroatoms selected from N, O and S, and optionally substituted with halo or C_{1-6} alkyl; C_{3-6} cycloalkyl; or R₃ and R₄ together with the N atom, when present, form a cyclic ring structure comprising 5-6 atoms selected from C, N, S and O; and

s is an integer from 0 to 8;

A is C_{5-12} aryl or C_{5-7} cycloalkyl, each optionally comprising 1 or more heteroatoms selected from N, S and O;

R₂ is H, amino, hydroxyl, halo, or straight or branched-chain C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} heteroalkyl, C_{1-6} aminoalkyl, C_{1-6} haloalkyl, C_{1-6} alkylthio, C_{1-6} alkoxycarbonyl, --CN, --CF₃, --OR₃, --COR₃, NO₂, --NHR₃, --NHC(O)R₃,

--C(O)NR₃ R₄, --NR₃ R₄, --NR₃ C(O)NR₄ R₅, --OC(O)R₃, --C(O)R₃ R₄, --O(CH₂)_q NR₃, -
-CNR₃ R₄ or --(CH₂)_q NR₃ R₄;

where q is an integer from 1 to 6;

n is 0, 1, 2, 3 or 4, the groups R₂, when n>1, being the same or different;

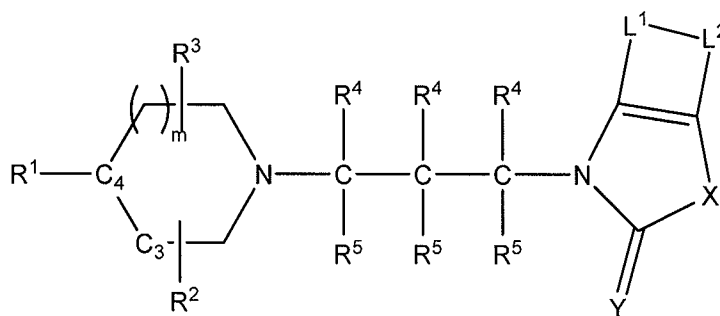
p is 0 or an integer from 1 to 5;

Y is O, S, CHOH, --NHC(O)--, --C(O)NH--, --C(O)--, --OC(O)--, NR₇ or --
CH=N--, and

R₇ is H or C₁₋₄ alkyl; or absent; and

Z is CR₈ R₉ wherein R₈ and R₉ are independently selected from H, and straight or
branched chain C₁₋₈ alkyl; or a pharmaceutically acceptable salt, ester or prodrug thereof.

17. (NEW) The method of claim 1, wherein the compound has the structure of
formula (V):



(V)

wherein

R¹ is a monoradical selected from the group consisting of optionally substituted
C₁₋₆-alkyl, optionally substituted C₂₋₆-alkylidene, optionally substituted C₂₋₆-alkenyl,
optionally substituted C₂₋₆-alkynyl, optionally substituted O—C₁₋₆-alkyl, optionally
substituted O—C₂₋₆-alkenyl, optionally substituted O—C₂₋₆-alkynyl; optionally
substituted S—C₁₋₆-alkyl, optionally substituted S—C₂₋₆-alkenyl, optionally substituted
S—C₂₋₆-alkynyl;

m is 0, 1 or 2;

C₃-C₄ is CH₂—CH or CH=C or C₄ is CH and C₃ is absent;

R² and R³ are independently selected from the group consisting of hydrogen,
optionally substituted C₁₋₆ alkyl, optionally substituted O—C₁₋₆ alkyl, halogen, hydroxy or
selected such that R² and R³ together form a ring system;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, halogen, hydroxy, optionally substituted C_{1-6} -alkyl, optionally substituted $O-C_{1-6}$ alkyl, optionally substituted aryl- C_{1-6} alkyl, and optionally substituted arylheteroalkyl;

L^1 and L^2 are biradicals independently selected from the group consisting of $-C(R^6)=C(R^7)-$, $-C(R^6)=N-$, $-N=C(R^6)-$, $-S-$, $-NH-$ and $-O-$; wherein only one of L^1 and L^2 may be selected from the group consisting of $-S-$, $-NH-$ and $-O-$;

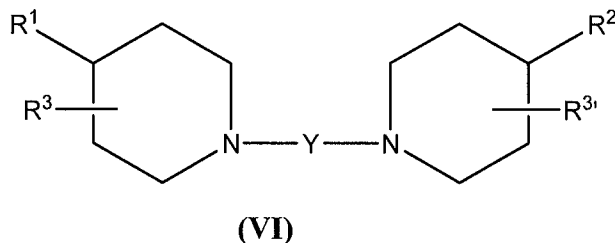
Y is selected from the group consisting of O, S, and H_2 ;

X is a biradical selected from the group consisting of $-C(R^6)(R^7)-C(R^6)(R^7)-$, $-C(R^6)=C(R^7)-$, $-O-C(R^6)(R^7)-$, $C(R^6)(R^7)-O-$, $-S-C(R^6)(R^7)-$, $-C(R^6)(R^7)-S-$, $-N(R^N)-C(R^6)(R^7)-$, $-C(R^6)(R^7)-N(R^N)-$, $-C(R^6)(R^7)-C(R^6)(R^7)-C(R^6)(R^7)-$, $-O-C(R^6)(R^7)-C(R^6)(R^7)-$, $S-C(R^6)(R^7)-C(R^6)(R^7)-$, $N(R^N)-C(R^6)(R^7)-C(R^6)(R^7)-$, $-C(R^6)(R^7)-C(R^6)(R^7)-O$, $-C(R^6)(R^7)-C(R^6)(R^7)-S$, $-C(R^6)(R^7)-C(R^6)(R^7)-N(R^N)-$, $-C(R^6)(R^7)-C(R^6)=C(R^7)-$, and $-C(R^6)=C(R^7)-C(R^6)(R^7)$,

wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, cyano, $NR^N R^N$, $N(R^N)-C(O)N(R^N)$, optionally substituted C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, , optionally substituted $O-C_{1-6}$ -alkyl, optionally substituted O-aryl, optionally substituted $O-C_{2-6}$ -alkenyl, optionally substituted $O-C_{2-6}$ -alkynyl, and

wherein R^N is selected from the group consisting of hydrogen, and optionally substituted C_{1-6} -alkyl.

18. (NEW) The method of claim 1, wherein the compound has the structure of formula (VI):



wherein

Y is a biradical of $(CR^4R^5)_m-Z-C(R^4R^5)_n$;

wherein the sum $m+n$ is from 1 to 7;

Z is selected from the group consisting of $C(R^4R^5)$, $C(O)$, O, $N(R^6)$, S, $O-C(O)$, $N(R^6)C(O)$, $C(O)-O$, and P; and

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, NR^6N^6 , optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{3-8} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted C_{1-6} -alkyl, optionally substituted C_{1-6} -alkoxy, optionally substituted phenoxy, optionally substituted C_{2-8} -alkenyl and optionally substituted C_{2-8} -alkynyl; and

wherein R^1 and R^2 are independently selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{3-8} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted C_{1-6} -alkyl, optionally substituted C_{1-6} -alkoxy, optionally substituted C_{2-8} -alkenyl and optionally substituted C_{2-8} -alkynyl;

wherein R^3 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, NR^6N^6 , optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{3-8} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted C_{1-6} -alkyl, optionally substituted C_{1-6} -alkoxy, optionally substituted C_{2-8} -alkenyl and optionally substituted C_{2-8} -alkynyl; and

R^6 and R^6 are independently selected from the group consisting of hydrogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{3-8} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted C_{1-6} -alkyl, optionally substituted C_{1-6} -alkoxy, optionally substituted C_{2-8} -alkenyl and optionally substituted C_{2-8} -alkynyl.